

United States Patent Application for:

Aerosolization Apparatus with Capsule Puncture Alignment Guide

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Aerosolization Apparatus with Capsule Puncture Alignment Guide

5 This application claims the benefit U.S. Provisional Patent Application Serial No. 60/461,748 filed on April 9, 2003, which is incorporated herein by reference in its entirety.

BACKGROUND

10 The need for effective therapeutic treatment of patients has resulted in the development of a variety of techniques for delivering a pharmaceutical formulation to a patient. One traditional technique involves the oral delivery of a pharmaceutical formulation in the form of a pill, capsule, or the like. Inhaleable drug delivery, where an aerosolized pharmaceutical formulation is orally or nasally inhaled by a patient to deliver the formulation to the patient's
15 respiratory tract, has also proven to be an effective manner of delivery. In one inhalation technique, a pharmaceutical formulation is delivered deep within a patient's lungs where it may be absorbed into the blood stream. In another inhalation technique, a pharmaceutical formulation is delivered locally to a particular site, such as an infected lung. Many types of inhalation devices exist including devices that aerosolize a dry powder pharmaceutical formulation.

20 One type of inhalation device aerosolizes a pharmaceutical formulation that is stored in a capsule. For example, a dose or a portion of a dose of a dry powder pharmaceutical formulation may be stored in a capsule, and the capsule may be inserted into an aerosolization device which is capable of aerosolizing the pharmaceutical formulation. The aerosolization may be
25 accomplished by releasing stored energy. For example, the aerosolization may be accomplished by utilizing energy supplied during the user's inhalation, such as the flow of inhaled air, to aerosolize the pharmaceutical formulation.

30 Before, during or after being inserted into the aerosolization device, the capsule is opened to expose the pharmaceutical formulation. The opening of the capsule may be performed, for example, by puncturing the capsule, tearing the capsule, or separating the parts of the capsule.

When the capsule is properly opened and when aerosolization energy is supplied, the pharmaceutical formulation is aerosolized so that it may be inhaled by the user and a dose or portion of a dose of the aerosolized pharmaceutical formulation may be delivered to the user's respiratory tract.

However, improper use of the aerosolization device may result in the delivery of less than the desired amount of the pharmaceutical formulation. For example, if a capsule is not properly or completely opened before the aerosolization process, the amount of pharmaceutical formulation being aerosolized may be reduced or the flow of the aerosolized pharmaceutical formulation may not be of sufficiently high quality to deliver a desirable amount to the user. In addition, residual pharmaceutical formulation within the aerosolization apparatus can limit the effectiveness of the capsule puncturing process.

Therefore, it is desirable to be able to improve the effectiveness and reproducibility of a capsule opening mechanism for an aerosolization apparatus. It is further desirable to be able to provide such capsule opening in a manner than increases the lifetime of the aerosolization apparatus.

SUMMARY

The present invention satisfies these needs. In one aspect of the invention, a capsule puncturing mechanism has a capsule alignment guide that improves the quality and consistency of capsule punctures. Additionally, the alignment guide extends the lifetime of the aerosolization apparatus.

In another aspect of the invention, an aerosolization apparatus comprises a housing defining a chamber having one or more air inlets, the chamber being sized to receive a capsule which contains an aerosolizable pharmaceutical formulation; a puncturing mechanism within the housing, the puncturing mechanism comprising an alignment guide and a puncture member, wherein the alignment guide comprises a surface adapted to contact the capsule while the puncture

member is advanced into the capsule to create an opening in the capsule, and wherein at least a portion of the surface is sloped at an angle which is less than 55 degrees relative to the longitudinal axis of the capsule; and an end section associated with the housing, the end section sized and shaped to be received in a user's mouth or nose so that the user may inhale through the end section to inhale aerosolized pharmaceutical formulation that has exited the capsule through the opening created in the capsule.

In another aspect of the invention, an aerosolization apparatus comprises a housing defining a chamber having one or more air inlets, the chamber being sized to receive a capsule which contains an aerosolizable pharmaceutical formulation; a puncturing mechanism within the housing, the puncturing mechanism comprising an alignment guide and a puncture member, wherein the alignment guide comprises a surface adapted to contact the capsule while the puncture member is advanced into the capsule to create an opening in the capsule, and wherein the surface comprises one or more protrusions for contacting the capsule; and an end section associated with the housing, the end section sized and shaped to be received in a user's mouth or nose so that the user may inhale through the end section to inhale aerosolized pharmaceutical formulation that has exited the capsule through the opening created in the capsule.

In another aspect of the invention, a method of providing access to an aerosolizable pharmaceutical formulation comprises providing a capsule containing an aerosolizable pharmaceutical formulation; contacting the capsule with the surface of an alignment guide, the surface being sloped at an angle which is less than 55 degrees relative to the longitudinal axis of the capsule; and advancing a puncture member through the wall of the capsule to create an opening in the capsule.

In another aspect of the invention, a method of providing access to an aerosolizable pharmaceutical formulation comprises providing a capsule containing an aerosolizable pharmaceutical formulation; contacting the capsule with the surface of an alignment guide, the surface comprising one or more protrusions for contacting the capsule; and advancing a puncture member through the wall of the capsule to create an opening in the capsule.

In another aspect of the invention, a method of aerosolizing a pharmaceutical formulation comprises inserting a capsule containing an aerosolizable pharmaceutical formulation in a chamber; contacting the capsule with the surface of an alignment guide, the surface being sloped at an angle which is less than 55 degrees relative to the longitudinal axis of the capsule and/or having one or more protrusions for contacting the capsule; advancing a puncture member through the wall of the capsule to create an opening in the capsule; aerosolizing the pharmaceutical formulation in the capsule by flowing air through the chamber; and administering the aerosolized pharmaceutical formulation to the respiratory tract of a user during the user's inhalation.

DRAWINGS

These features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings which illustrate exemplary features of the invention. However, it is to be understood that each of the features can be used in the invention in general, not merely in the context of the particular drawings, and the invention includes any combination of these features, where:

Figure 1A is a schematic sectional side view of a version of an aerosolization apparatus in a rest position;

Figure 1B is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 1A just before capsule puncture;

Figure 1C is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 1A as the capsule is being punctured;

Figure 1D is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 1A just after capsule puncture;

Figure 1E is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 1A in use;

Figure 2A is a schematic sectional side view of another version of an aerosolization apparatus in a rest position;

Figure 2B is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 2A just before capsule puncture;

Figure 2C is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 2A as the capsule is being punctured;

Figure 2D is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 2A just after capsule puncture;

Figure 2E is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 2A in use;

Figure 3 is a graph showing the effectiveness of using an alignment guide according to the present invention; and

Figure 4 is a schematic perspective view of a version of an alignment guide.

DESCRIPTION

The present invention relates to an aerosolization apparatus. In particular, the invention relates to an aerosolization apparatus capable of aerosolizing a powder contained in a capsule. Although the process is illustrated in the context of aerosolizing a dry powder pharmaceutical formulation for inhalation, the present invention can be used in other processes and should not be limited to the examples provided herein.

An aerosolization apparatus **100** according to the present invention is shown schematically in Figure 1A. The aerosolization apparatus **100** comprises a housing **105** defining a chamber **110** having one or more air inlets **115** and one or more air outlets **120**. The chamber **110** is sized to receive a capsule **125** which contains an aerosolizable pharmaceutical formulation. A puncturing mechanism **130** comprises an alignment guide **132** having a seating surface **133** and a passageway **134** in which a puncture member **135** is slidably received. Near or adjacent the outlet **120** is an end section **140** that may be sized and shaped to be received in a user's mouth or nose so that the user may inhale through an opening **145** in the end section **140** that is in communication with the outlet **120**.

The aerosolization apparatus **100** utilizes air flowing through the chamber **110** to aerosolize the pharmaceutical formulation in the capsule **125**. For example, Figures 1A through 1E illustrate the operation of a version of an aerosolization apparatus **100** where air flowing through the inlet **115** is used to aerosolize the pharmaceutical formulation and the aerosolized pharmaceutical formulation flows through the outlet **120** so that it may be delivered to the user through the opening **145** in the end section **140**. The aerosolization apparatus **100** is shown in its initial condition in Figure 1A. The capsule **125** is positioned within the chamber **110** and the pharmaceutical formulation is contained within the capsule **125**.

To use the aerosolization apparatus **100**, the pharmaceutical formulation in the capsule **125** is exposed to allow it to be aerosolized. In the version of Figures 1A through 1E, the puncture mechanism **130** is advanced within the chamber **110** by applying a force **150** to the puncture mechanism **130**. Initially, the alignment guide **132** and the puncture member **135** advance as a unit to the position shown in Figure 1B. In this position, the seating surface **133** contacts the capsule **125** to center the capsule **125** on the alignment guide **132**. For example, a user may press against a surface of the puncturing mechanism **130** to cause the puncturing mechanism **130** to slide within the housing **105**. By continuing to apply the force **150**, the puncture member **135** is advanced into and through the wall of the capsule **125**, as shown in Figure 1C. The puncture member may comprise one or more sharpened tips **152** to facilitate the advancement through the wall of the capsule **125**. The puncturing mechanism **130** is then retracted to the position shown in

Figure 1D, leaving an opening **160** through the wall of the capsule **125** to expose the pharmaceutical formulation in the capsule **125**.

Air or other gas then flows through an inlet **115**, as shown by arrows **165** in Figure 1E. The flow of air causes the pharmaceutical formulation to be aerosolized. When the user inhales **170** through the end section **140** the aerosolized pharmaceutical formulation is delivered to the user's respiratory tract. In one version, the air flow **165** may be caused by the user's inhalation **170**. In another version, compressed air or other gas may be ejected into the inlet **115** to cause the aerosolizing air flow **165**.

Proper creation of the opening **160** in the capsule **125** allows for efficient and effective delivery of the aerosolized pharmaceutical formulation to the user. In contrast, improper creation of the opening **160** can lead to inefficient and less effective delivery of the medicament to a user. Therefore a properly sharpened tip **152** can help in the creation of consistent openings in the capsule. Also, it is important to have the sharpened tip **152** properly aligned with the capsule **125** to assure proper creation of the opening **160**.

Accordingly, to increase the efficiency and effectiveness of the aerosolization apparatus **100**, the alignment guide **132** may be designed to improve capsule alignment. In one version, the seating surface **133** is positioned so that at least a portion of the surface is at an angle, a , relative to a transverse axis of greater than 35 degrees, more preferably from 35 degrees to 55 degrees, more preferably from 40 degrees to 53 degrees, and most preferably about 45 degrees. Conventional alignment guides, such as those available from PH&T Pharma in Milan, Italy, and those described in PCT application WO 02/083220 which is incorporated herein by reference in its entirety, have an angle, a , less than 33 degrees. The increased angle, a , of the seating surface **133** provides a decreased angle, b , relative to the longitudinal axis of the capsule **125** and/or the longitudinal axis of the chamber **110** and/or the longitudinal axis of the puncture member **135**. The angle, b , of the seating surface **133** relative to one or more of these axes is preferably less than 55 degrees, more preferably from 35 degrees to 55 degrees, more preferably from 37 degrees to 50 degrees, and most preferably about 45 degrees. It has been unexpectedly discovered, that the

increased angle, α , of the seating surface **133** significantly improves capsule alignment and unexpectedly extends the effective lifetime of the aerosolization apparatus **100**.

A version of an aerosolization apparatus **100** comprising an alignment guide **132** according to the present invention is shown in Figures 2A through 2E. In this version, the housing **105** of the aerosolization apparatus **100** comprises a body **205** and a removable endpiece **210**. The endpiece **210** may be removed from the body **205** to insert a capsule **125** in the chamber **110** which is formed when the body **205** and the endpiece **210** are connected together. The endpiece **210** comprises a partition **215** that blocks the forward end of the chamber **110**, and the partition **215** has the one or more outlets **120** extending therethrough. An example of an aerosolization apparatus with a partition **215** and chamber **110** is described in U.S. Patent 4,069,819 and in U.S. Patent 4,995,385, both of which are incorporated herein by reference in their entireties. In such an arrangement, the chamber **110** comprises a longitudinal axis that lies generally in the inhalation direction, and the capsule **125** is insertable lengthwise into the chamber **110** so that the capsule's longitudinal axis may be parallel to the longitudinal axis of the chamber **110**. In the version of Figures 2A through 2E, the chamber **110** is sized to receive a capsule **125** containing a pharmaceutical formulation in a manner which allows the capsule to move within the chamber **110**. The inlets **115** comprise a plurality of tangentially oriented slots **220**. When a user inhales **170** through the endpiece **210**, outside air is caused to flow through the tangential slots **220** as shown by arrows **225** in Figure 2E. This airflow **225** creates a swirling airflow within the chamber **110**. The swirling airflow causes the capsule **125** to contact the partition **215** and then to move within the chamber **110** in a manner that causes the pharmaceutical formulation to exit the capsule **125** and become entrained within the swirling airflow. In one version, the capsule **125** may rotate within the chamber **110** in a manner where the longitudinal axis of the capsule is remains at an angle less than 80 degrees, and preferably less than 45 degrees from the longitudinal axis of the chamber. The movement of the capsule **125** in the chamber **110** may be caused by the width of the chamber **110** being less than the length of the capsule **125**. In one specific version, the chamber **110** comprises a tapered section **230** that terminates at an edge **235**. During the flow of swirling air in the chamber **110**, the forward end of the capsule **125** contacts and rests on the partition **215** and a sidewall of the capsule **125** contacts the edge **235** and slides and/or rotates along the edge **235**. This motion of the

capsule is particularly effective in forcing a large amount of the pharmaceutical formulation through one or more openings **160** in the rear of the capsule **125**.

The one or more openings **160** in the rear of the capsule **125** in the version of
5 Figures 2A through 2E are created by a puncturing mechanism **130** having a puncture member **135**
such as any of those described above that is slidable within the body **205**. The puncturing
mechanism **130**, shown in its rest position in Figure 2A, comprises a plunger **240** attached at its
forward end **245** to the puncture member **135**, which in the version shown is a U-shaped staple **250**
having two sharpened tips **152** as in any version described above or the like. The puncturing
10 mechanism **130** further comprises an alignment member **255** which contacts the plunger **240** and/or
the puncture member **135** and is slidable relative to the plunger **240** and the puncture member **135**.
To create the openings **160** in the capsule **125**, the user applies a force **150** to the plunger **240**, as
shown in Figure 2B, such as by pressing against the end surface **155** of the plunger **240** with the
user's finger or thumb. The force **150** causes the plunger to slide within the body **205**. A slight
15 frictional contact between the plunger **240** the a rear section **260** of the alignment member **255**
causes the alignment member **255** to also slide within the body **205** until a forward seating surface
265 of the alignment member **255** contacts the capsule **125**, as shown in Figure 2B. The forward
seating surface **265**, which may be angled at an angle, α , as discussed above, contacts capsule **125**
and secures the capsule **125** between the alignment member **255** and the partition **215**. The
20 continued application of force **150** causes the plunger **240** and the puncture member **135** to slide
relative to the alignment member **255**, as shown in Figure 2C, to advance the puncture member **135**
through openings **270** in the forward seating surface **265** and into the capsule **125**. Upon the
removal of the force **150**, a spring **275** or other biasing member urges the puncturing mechanism
130 back to its rest position. For example, the spring **275** may contact a shoulder **280** in the body
25 **205** and press a flange **285** on the plunger **240** toward a rim **290** in the body **205**. The frictional
engagement between the plunger **240** and the alignment member **255** also returns the alignment
member **255** to its retracted position when the plunger is returned to its retracted position.

In another version, the aerosolization apparatus **100** may be configured differently
30 than as shown in Figures 1A through 1D and 2A through 2E. For example, the chamber **100** may
be sized and shaped to receive the capsule **125** so that the capsule **125** is orthogonal to the

inhalation direction, as described in U.S. Patent 3,991,761. As also described in U.S. Patent 3,991,761, the puncturing mechanism **130** may puncture both ends of the capsule **125**. In such version, the puncture member **135** of the present invention may be provided to puncture one or both ends of the capsule **125**. In another version, the chamber may receive the capsule **125** in a manner where air flows through the capsule **125** as described for example in U.S. Patent 4,338,931 and in U.S. Patent 5,619,985. In another version, the aerosolization of the pharmaceutical formulation may be accomplished by pressurized gas flowing through the inlets, as described for example in US Patent 5,458,135, U.S. Patent 5,785,049, and U.S. Patent 6,257,233, or propellant, as described in PCT Publication WO 00/72904 and U.S. Patent 4,114,615. All of the above references being incorporated herein by reference in their entireties.

Figure 3 graphically illustrates the advantages using an alignment guide **132** according to the present invention. The diamonds show the resulting emitted dose using a conventional alignment guide having a seating surface with an angle, α , less than 33 degrees. As can be seen, the device loses effectiveness after about 20 actuations. However, the alignment guide having a seating surface having an angle, α , of about 45 degrees provides effective use even after 80 actuations, as shown by the circles and squares.

Another version of an alignment guide **132** is shown in Figure 4. In this version, the seating surface **133** comprises one or more protrusions, such as ribs **300**, that serve to contact the capsule during the puncturing process. The ribs **300** create troughs **305** into which residual powder pharmaceutical formulation may deposit. By providing the troughs **305** and thereby reducing the amount of residual powder on the portion of the seating surface **133** that contacts the capsule, the effectiveness of the aerosolization apparatus is improved and the lifetime of the aerosolization apparatus is extended. The ribs **300** may extend longitudinally, as shown, and/or may extend in an orthogonal direction. In one version, longitudinally extending ribs **300**, as shown, are at an angle, α , as described above. The surface of the seating surface **133** and/or the ribs **300** may comprise a low friction material to further reduce the wear on the surface. Alternatively or additionally, the protrusions may be in the form of other raised portions such as bumps and/or the troughs may be formed by indentations, such as divots or valleys, into the surface.

In a preferred version, the invention provides a system and method for aerosolizing a pharmaceutical formulation and delivering the pharmaceutical formulation to the respiratory tract of the user, and in particular to the lungs of the user. The pharmaceutical formulation may comprise powdered medicaments, liquid solutions or suspensions, and the like, and may include an active agent.

The active agent described herein includes an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vaccines, vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient. An active agent for incorporation in the pharmaceutical formulation described herein may be an inorganic or an organic compound, including, without limitation, drugs which act on: the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system, and the central nervous system. Suitable active agents may be selected from, for example, hypnotics and sedatives, psychic energizers, tranquilizers, respiratory drugs, anticonvulsants, muscle relaxants, antiparkinson agents (dopamine antagonists), analgesics, anti-inflammatories, antianxiety drugs (anxiolytics), appetite suppressants, antimigraine agents, muscle contractants, anti-infectives (antibiotics, antivirals, antifungals, vaccines) antiarthritics, antimalarials, antiemetics, antiepileptics, bronchodilators, cytokines, growth factors, anti-cancer agents, antithrombotic agents, antihypertensives, cardiovascular drugs, antiarrhythmics, antioxidants, anti-asthma agents, hormonal agents including contraceptives, sympathomimetics, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, anticoagulants, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, antienteritis agents, vaccines, antibodies, diagnostic agents, and contrasting agents. The active agent, when administered by inhalation, may act locally or systemically.

The active agent may fall into one of a number of structural classes, including but

not limited to small molecules, peptides, polypeptides, proteins, polysaccharides, steroids, proteins capable of eliciting physiological effects, nucleotides, oligonucleotides, polynucleotides, fats, electrolytes, and the like.

5 Examples of active agents suitable for use in this invention include but are not limited to one or more of calcitonin, amphotericin B, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporin, granulocyte colony stimulating factor (GCSF), thrombopoietin (TPO), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, 10 interferon gamma, interleukin-1 receptor, interleukin-2, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, luteinizing hormone releasing hormone (LHRH), factor IX, insulin, pro-insulin, insulin analogues (e.g., mono-acylated insulin as described in U.S. Patent No. 5,922,675, which is incorporated herein by reference in its entirety), amylin, C-peptide, 15 somatostatin, somatostatin analogs including octreotide, vasopressin, follicle stimulating hormone (FSH), insulin-like growth factor (IGF), insulintropin, macrophage colony stimulating factor (M-CSF), nerve growth factor (NGF), tissue growth factors, keratinocyte growth factor (KGF), glial growth factor (GGF), tumor necrosis factor (TNF), endothelial growth factors, parathyroid hormone (PTH), glucagon-like peptide thymosin alpha 1, IIB/IIIa inhibitor, alpha-1 antitrypsin, 20 phosphodiesterase (PDE) compounds, VLA-4 inhibitors, bisphosphonates, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyribonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, 13-cis retinoic acid, macrolides such as erythromycin, oleandomycin, troleandomycin, roxithromycin, clarithromycin, davercin, azithromycin, flurithromycin, dirithromycin, josamycin, spiromycin, midecamycin, 25 leucomycin, miocamycin, rokitamycin, andazithromycin, and swinolide A; fluoroquinolones such as ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, alatrofloxacin, moxifloxacin, norfloxacin, enoxacin, grepafloxacin, gatifloxacin, lomefloxacin, sparfloxacin, temafloxacin, pefloxacin, amifloxacin, fleroxacin, tosufloxacin, prulifloxacin, irloxacin, pazufloxacin, clinafloxacin, and sitafloxacin, aminoglycosides such as gentamicin, netilmicin, paramecin, tobramycin, amikacin, 30 kanamycin, neomycin, and streptomycin, vancomycin, teicoplanin, rampolanin, mideplanin, colistin, daptomycin, gramicidin, colistimethate, polymixins such as polymixin B, capreomycin,

5 bacitracin, penems; penicillins including penicillinase-sensitive agents like penicillin G, penicillin V, penicillinase-resistant agents like methicillin, oxacillin, cloxacillin, dicloxacillin, floxacillin, nafcillin; gram negative microorganism active agents like ampicillin, amoxicillin, and hetacillin, cillin, and galampicillin; antipseudomonal penicillins like carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin; cephalosporins like cefpodoxime, cefprozil, ceftbuten, ceftizoxime, ceftriaxone, cephalothin, cephapirin, cephalixin, cephradine, cefoxitin, cefamandole, cefazolin, cephaloridine, cefaclor, cefadroxil, cephaloglycin, cefuroxime, ceforanide, cefotaxime, cefatrizine, cephacetrile, cefepime, cefixime, cefonicid, cefoperazone, cefotetan, cefmetazole, ceftazidime, loracarbef, and moxalactam, monobactams like aztreonam; and carbapenems such as imipenem, meropenem, pentamidine isethiouate, albuterol sulfate, lidocaine, metaproterenol sulfate, beclomethasone diprepionate, triamcinolone acetamide, budesonide acetoneide, fluticasone, ipratropium bromide, flunisolide, cromolyn sodium, ergotamine tartrate and where applicable, analogues, agonists, antagonists, inhibitors, and pharmaceutically acceptable salt forms of the above. In reference to peptides and proteins, the invention is intended to encompass synthetic, native, glycosylated, unglycosylated, pegylated forms, and biologically active fragments and analogs thereof.

20 Active agents for use in the invention further include nucleic acids, as bare nucleic acid molecules, vectors, associated viral particles, plasmid DNA or RNA or other nucleic acid constructions of a type suitable for transfection or transformation of cells, i.e., suitable for gene therapy including antisense. Further, an active agent may comprise live attenuated or killed viruses suitable for use as vaccines. Other useful drugs include those listed within the Physician's Desk Reference (most recent edition).

25 The amount of active agent in the pharmaceutical formulation will be that amount necessary to deliver a therapeutically effective amount of the active agent per unit dose to achieve the desired result. In practice, this will vary widely depending upon the particular agent, its activity, the severity of the condition to be treated, the patient population, dosing requirements, and the desired therapeutic effect. The composition will generally contain anywhere from about 1% by weight to about 99% by weight active agent, typically from about 2% to about 95% by weight active agent, and more typically from about 5% to 85% by weight active agent, and will also

depend upon the relative amounts of additives contained in the composition. The compositions of the invention are particularly useful for active agents that are delivered in doses of from 0.001 mg/day to 100 mg/day, preferably in doses from 0.01 mg/day to 75 mg/day, and more preferably in doses from 0.10 mg/day to 50 mg/day. It is to be understood that more than one active agent may be incorporated into the formulations described herein and that the use of the term "agent" in no way excludes the use of two or more such agents.

The pharmaceutical formulation may comprise a pharmaceutically acceptable excipient or carrier which may be taken into the lungs with no significant adverse toxicological effects to the subject, and particularly to the lungs of the subject. In addition to the active agent, a pharmaceutical formulation may optionally include one or more pharmaceutical excipients which are suitable for pulmonary administration. These excipients, if present, are generally present in the composition in amounts ranging from about 0.01 % to about 95% percent by weight, preferably from about 0.5 to about 80%, and more preferably from about 1 to about 60% by weight. Preferably, such excipients will, in part, serve to further improve the features of the active agent composition, for example by providing more efficient and reproducible delivery of the active agent, improving the handling characteristics of powders, such as flowability and consistency, and/or facilitating manufacturing and filling of unit dosage forms. In particular, excipient materials can often function to further improve the physical and chemical stability of the active agent, minimize the residual moisture content and hinder moisture uptake, and to enhance particle size, degree of aggregation, particle surface properties, such as rugosity, ease of inhalation, and the targeting of particles to the lung. One or more excipients may also be provided to serve as bulking agents when it is desired to reduce the concentration of active agent in the formulation.

Pharmaceutical excipients and additives useful in the present pharmaceutical formulation include but are not limited to amino acids, peptides, proteins, non-biological polymers, biological polymers, carbohydrates, such as sugars, derivatized sugars such as alditols, aldonic acids, esterified sugars, and sugar polymers, which may be present singly or in combination. Suitable excipients are those provided in WO 96/32096, which is incorporated herein by reference in its entirety. The excipient may have a glass transition temperature (T_g) above about 35° C, preferably above about 40 °C, more preferably above 45° C, most preferably above about 55 °C.

Exemplary protein excipients include albumins such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. Suitable amino acids (outside of the dileucyl-peptides of the invention), which may also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, tyrosine, tryptophan, and the like. Preferred are amino acids and polypeptides that function as dispersing agents. Amino acids falling into this category include hydrophobic amino acids such as leucine, valine, isoleucine, tryptophan, alanine, methionine, phenylalanine, tyrosine, histidine, and proline. Dispersibility-enhancing peptide excipients include dimers, trimers, tetramers, and pentamers comprising one or more hydrophobic amino acid components such as those described above.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), pyranosyl sorbitol, myoinositol and the like.

The pharmaceutical formulation may also include a buffer or a pH adjusting agent, typically a salt prepared from an organic acid or base. Representative buffers include organic acid salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid, Tris, tromethamine hydrochloride, or phosphate buffers.

The pharmaceutical formulation may also include polymeric excipients/additives, e.g., polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, Ficolls (a polymeric sugar), hydroxyethylstarch, dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl- β -cyclodextrin and sulfobutylether- β -cyclodextrin), polyethylene glycols, and pectin.

The pharmaceutical formulation may further include flavoring agents, taste-masking agents, inorganic salts (for example sodium chloride), antimicrobial agents (for example

benzalkonium chloride), sweeteners, antioxidants, antistatic agents, surfactants (for example polysorbates such as "TWEEN 20" and "TWEEN 80"), sorbitan esters, lipids (for example phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines), fatty acids and fatty esters, steroids (for example cholesterol), and chelating agents (for example EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the invention are listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), both of which are incorporated herein by reference in their entireties.

"Mass median diameter" or "MMD" is a measure of mean particle size, since the powders of the invention are generally polydisperse (i.e., consist of a range of particle sizes). MMD values as reported herein are determined by centrifugal sedimentation, although any number of commonly employed techniques can be used for measuring mean particle size. "Mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior, and is the diameter of a unit density sphere having the same settling velocity, generally in air, as the particle. The aerodynamic diameter encompasses particle shape, density and physical size of a particle. As used herein, MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction.

In one version, the powdered formulation for use in the present invention includes a dry powder having a particle size selected to permit penetration into the alveoli of the lungs, that is, preferably 10 μm mass median diameter (MMD), preferably less than 7.5 μm , and most preferably less than 5 μm , and usually being in the range of 0.1 μm to 5 μm in diameter. The delivered dose efficiency (DDE) of these powders may be greater than 30%, more preferably greater than 40%, more preferably greater than 50% and most preferably greater than 60% and the aerosol particle size distribution is about 1.0 - 5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5 - 4.5 μm MMAD and preferably 1.5 - 4.0 μm MMAD. These dry powders have a moisture content below about 10% by weight, usually below about 5% by weight, and preferably below about 3% by weight. Such powders are described in WO 95/24183, WO

96/32149, WO 99/16419, and WO 99/16422, all of which are all incorporated herein by reference in their entirety.

In one version, as discussed above, the pharmaceutical formulation may be contained within a capsule **125**. The capsule **125** may be of a suitable shape, size, and material to contain the pharmaceutical formulation and to provide the pharmaceutical formulation in a usable condition. For example, the capsule may comprise a wall which comprises a material that does not adversely react with the pharmaceutical formulation. In addition, the wall may comprise a material that allows the capsule to be opened to allow the pharmaceutical formulation to be aerosolized. In one version, the wall comprises one or more of gelatin, hydroxypropyl methylcellulose (HPMC), polyethyleneglycol-compounded HPMC, hydroxypropylcellulose, agar, or the like. In one version, the capsule may comprise telescopically adjoining sections, as described for example in U.S. Patent 4,247,066 which is incorporated herein by reference in its entirety. The size of the capsule may be selected to adequately contain the dose of the pharmaceutical formulation. The sizes generally range from size 5 to size 000 with the outer diameters ranging from about 4.91 mm to 9.97 mm, the heights ranging from about 11.10 mm to about 26.14 mm, and the volumes ranging from about 0.13 ml to about 1.37 ml, respectively. Suitable capsules are available commercially from, for example, Shionogi Qualicaps Co. in Nara, Japan and Capsugel in Greenwood, South Carolina. After filling, a top portion may be placed over the bottom portion to form the a capsule shape and to contain the powder within the capsule, as described in U.S. Patent 4,846,876, U.S. Patent 6,357,490, and in the PCT application WO 00/07572 published on February 17, 2000, all of which are incorporated herein by reference in their entirety.

Although the present invention has been described in considerable detail with regard to certain preferred versions thereof, other versions are possible, and alterations, permutations and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification and study of the drawings. For example, the cooperating components may be reversed or provided in additional or fewer number. Also, the various features of the versions herein can be combined in various ways to provide additional versions of the present invention. Furthermore, certain terminology has been used for the purposes of descriptive clarity, and not to limit the present invention. Therefore, any appended claims should not be limited to the description

of the preferred versions contained herein and should include all such alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.